The Wenzhou FGF team: zooming in on the therapeutic applications of FGFs in China

The fibroblast growth factor (FGF) family is comprised of a group of structurally related protein ligands that signal through FGF receptor tyrosine kinases (FGFRs) to carry out a plethora of vital functions in development, metabolism, tissue homeostasis and repair after injury. Historically, translational research of FGF/FGFR has focused on the oncology aspect in the West, whereas the research team led by Prof. Xiaokun Li based at both Wenzhou Medical University and Wenzhou University is devoted to FGF biotechnology and the delivery of engineered clinical grade FGFs for tissue repair and regeneration.

The FGF family consists of 18 mammalian FGFs divided into 6 subgroups on the bases of their sequence homology, phylogenetics and structural characteristics. Five of the subgroups are considered canonical FGFs capable of high affinity binding to heparin sulfate (HS) and acting locally as paracrine molecules. The potential of FGFs in promoting cell proliferation, survival, angiogenesis, migration, and differentiation, have been explored for therapeutic applications in the setting of tissue repair/regeneration and also cancer therapy. Li' s team, which started from Jinan University, Guangzhou, overcame several major bottlenecks for FGF protein engineering and recombinant production such as poor protein solubility and stability, enabling them to develop and license the first FGF protein drug (FGF2) in the world for clinical use. The clinical trial of the topical FGF2 biologics, led by Prof. Xiaobing Fu and first reported in the Lancet, proved its beneficial effect in accelerating healing of burn wound, skin flap transplantation, and diabetic ulcers. As of June 2017, in China alone, FGF biologics have been used in 80 million cumulative patients/cases with great clinical and socioeconomic benefit. Importantly, the safety record of this treatment has been excelling; during a 20-year period post-FGF treatment of clinical follow-up, no excessive hyperplasia or other major adverse effects have been observed. The FGF biologics have transformed the clinical practice of trauma management from the traditional anti-infection and anti-inflammation therapies to include FGF-induced coordinated pro-active repair and functional regeneration. In the past 10 years, Li and his colleagues have also successfully developed novel formulations for FGF1 and FGF2, as well as FGF7 and FGF10 biologics, which are currently in different phases of clinical evaluation.

The endocrine FGFs are relatively new members of the FGF family with much reduced affinity toward HS and activate FGFRs with Klotho as a cofactor and exhibit distinct regulatory activity in various metabolic processes including glucose, lipid, bile acid, vitamin D and phosphate metabolism and energy homeostasis. These atypical FGFs, as exemplified by FGF21, present therapeutic potentials for a myriad of major metabolic diseases such as diabetes, obesity, cardiovascular and renal diseases, amongst others. Besides the aforementioned paracrine FGFs, Li' s team has also undertaken major effort on basic and translational research on endocrine FGFs, particularly FGF21. Li and his colleagues first discovered the role of adiponectin in mediating the metabolic effect of FGF21 on energy metabolism and insulin sensitivity, as well as protection against atherosclerosis. Currently the team has completed preclinical studies and is in the process of applying for CFDA approval for clinical trial on FGF21 for the treatment of diabetes. In collaboration with Prof. Mohammadi from New York University, Li' s team provides structural insight into the activation of Phospholipase C by the concerted action of two FGF receptor molecules. More recent studies from Li' s team have unveiled unexpected therapeutic activity of FGF1 toward diabetic nephropathy and demonstrated that mitogenic and metabolic activities can be uncoupled by tuning FGF1/FGFR dimer stability. These mechanistic findings will likely lead to future drug discoveries targeting FGFs for the treatment of a variety of human diseases. A non-mitogenic mutant FGF1 formula is also under preclinical evaluation for the treatment of Type 2 Diabetes.

Over the past two decades, the Wenzhou FGF team has grown into one of the largest research team in the world exclusively dedicated to FGF basic and translational research with their clinical application as an ultimate goal. The therapeutic modalities using FGF formulations have evolved from the initial external and topical administration to implantable medical device as well as injection. The clinical indications have expanded from trauma and diabetic ulcer treatment, to neurological repair/regeneration. In the immediate future, FGFs will also be instrumental in the treatment of major metabolic diseases, such as diabetes and atherosclerosis. Armed with the rich and validated experience of "Chinese Style" protein drug development, the Wenzhou FGF team and its network of international collaborators, which together constitute the "Wenzhou FGF family" is pushing ahead to make significant contributions to translate FGF research discoveries into clinical application in the years to come.